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| EXAMINER |
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LOEWE, SUN JAE Y

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| ART UNIT | PAPER NUMBER |
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1609

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05/07/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/517,576 | ARRINGTON ET AL. | |
| | Examiner | Art Unit | |
| | Sun Jae Y. Loewe | 1609 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 March 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10, 20-23 and 27-33 is/are pending in the application.
- 4a) Of the above claim(s) 8-10, 20-23 and 27-33 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 5 and 6 is/are allowed.
- 6) ☒ Claim(s) 1-4 and 7 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>7/27/2007</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION***Election/Restrictions***

1. Applicant's election with traverse of Group I, and methyl 4-(2,5-difluorophenyl)-2-phenyl-2,5-dihydro-1H-pyrrole-1-carboxylate, in the reply filed on March 29, 2007 is acknowledged. The traversal is on the ground(s) that: (i) a special technical feature does exist because the genus of compounds claimed incorporate cyclic substituents at the 3- and 5-positions of a 1-oxycarbonylsubstituted 2,5-dihydropyrrole ring; and (ii) there would be no serious burden to search the inventions set forth in Groups I and II of the restriction requirement. The restriction requirement was thus stated to be improper. This is not found persuasive for the following two reasons.

First, it is noted that the core structure for the subgenus of compounds in claim 3 incorporates cyclic substituents at the 3- and 5- positions of a 2,5-dihydropyrrole ring. However, the compounds of claim 1 share a broader core structure defined only by a 5-membered heterocycle with a nitrogen atom. That is, all other structural features are variable. As was previously stated in the restriction requirement, a 5-membered heterocyclic ring with a nitrogen atom does not make a contribution over the prior art.

Second, because the instant case is a national stage application submitted under 35 U.S.C. 371, the Unity of Invention practice in MPEP § 1850 and MPEP § 1893.03(d) was followed, not restriction practice. Thus, the criteria for burden stated in MPEP § 803 does not apply.

The restriction requirement mailed on February 27, 2007 is still deemed proper and is made FINAL.

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2. Based on Applicant's species election, the search and examination was performed the core chemical structure defined in claim 3. MPEP 1893.03(d) states that when all of the claims drawn to the elected invention are allowable (i.e., meet the requirements of 35 U.S.C. 101, 102, 103 and 112), the nonelected invention(s) should be considered for rejoinder. The elected invention was not allowable under 35 U.S.C 112 (see below sections 6 and 7). Thus, the nonelected subject matter was not rejoined.

3. Claims 8-10, 20-23, 27-33 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions. Applicant timely traversed the restriction (election) requirement in the reply filed on March 29, 2007.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on April 19, 2006 was in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. Accordingly, the information disclosure statement was considered. A signed copy of form 1449 is enclosed herewith. The reference submitted for Ranjon et al. was not considered because an English language translation was not provided.

Claim Objections

5. Claims 1, 2, 7 are objected to for containing non-elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to

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enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4 and 7 are rejected under 35 USC 112 1st paragraph as failing to comply with the written description requirement.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

“To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that ‘the inventor invented the claimed invention.’ Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (“[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.”). Thus, an applicant complies with the written description requirement “by describing the invention, with all its claimed limitations, not that which makes it obvious,” and by using “such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.” Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.” *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

“A written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) (“In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...”) *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The Guidelines for Examination of Patent Applications Under 35 USC 112, ¶1, "Written Description" Requirement (Federal Register, Vol. 66, No. 4, pg. 1105, column 3), in accordance with MPEP § 2163, specifically states that for each claim drawn to a genus the written description requirement may be satisfied through sufficient description of a representative number of species by a) actual reduction to practice; b) reduction to drawings or structural chemical formulas; c) disclosure of relevant, identifying characteristics (ie. structure) by functional characteristics coupled with a known or disclosed correlation between function and structure. The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention (Federal Register, Vol. 66, No. 4, p. 1105, 3rd column, 3rd paragraph). Below is such comparison.

I. Scope of Claims (based on elected subject matter)

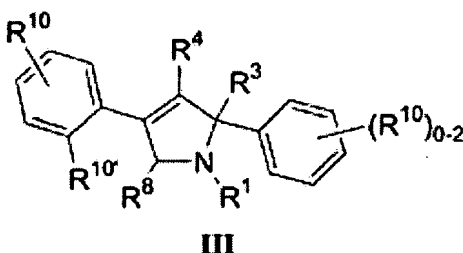
Claims 1-3, 7

Compounds of Formula III (see structure below), salt, stereoisomer, or pharmaceutical composition thereof; R¹, R³, R⁴, R⁸, R¹⁰, R^{10'} are as defined in claim 3

Claim 4

Compounds of Formula III (see structure below), salt, stereoisomer, or pharmaceutical composition thereof. The scope of variables R¹, R³, R⁴, R⁸ as claimed is congruent with the scope of the disclosure. R¹⁰, R^{10'} are as defined in claim 3

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II. Scope of Disclosure

Reduction to Practice: a *limited* set of compounds *representing* following substitutions,

- $R_1 =$ (C=O)O-C₁-C₁₀ alkyl (optionally substituted with amino, dimethylamino or alkyl)
 (C=O)O-phenyl (unsubstituted)
 (C=O)O-pyrrolidine or (C=O)O-piperidine (both unsubstituted)
 $R_{3,4,8} =$ H, Me
 $R_{10} =$ halogen
 $R_{10'} =$ halogen

Reduction to Structural or Chemical Formulas:

It is noted that the disclosure *lists* possible substituents for all the variables in Markush style. However, this type of disclosure is not viewed in the art to be a representation of any of the species it entails. A “laundry list” disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not “reasonably lead” those skilled in the art to any particular species. MPEP 2163.I.A. and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

Thus, there is no disclosure by reduction to structural/chemical formulas of species in addition to those reduced to practice.

Correlation between Structure and Function:

No correlation between structure and function is provided in the disclosure. Thus, it is not known what specific structural elements, shared by the genus of compounds claimed, are essential for the activity of these compounds as KSP inhibitors.

III. Analysis of Fulfillment of Written Description Requirement:

The structure/activity relationship (SAR) for binding and inhibition is elucidated upon analysis of IC₅₀ data of multiple compounds with various types of structural modifications. These studies, often in view of x-ray crystallographic data (see for example Fraley et al., p. 1777, 2nd column), provide insight into the structural limitations that are required for activity, ie. specific structural elements essential for the claimed activity. In the absence of such correlation, in view of the low predictability in the art, it is difficult to predict what structural modifications will allow for the preservation of the desired activity.

Particularly relevant to the current analysis is a SAR study of 3,5-diaryl-4,5-dihydropyrazole inhibitors of KSP which share structural similarity to the instantly claimed compounds. Modest modifications to a single substituent resulted in significant losses in potency or complete loss of activity, for example: fluorine to bromine/methyl/methoxy/trifluoromethyl (Cox et al., p. 2042, 1st column, 3rd paragraph); (C=O)Me to Me (Cox et al. p.2042, figure 1 and p. 2043, table 2, entry 13f).

Thus, absent a disclosure of the essential structural elements, one of ordinary skill would not have a reasonable expectation that the compounds not exemplified in the disclosure, which differ significantly from the subgenus exemplified, would possess the KSP inhibiting activity.

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In conclusion:

- (i) Substantial structural variation exists in the genus/subgenus embraced by claims 1-4,
7
- (ii) Disclosure of species supporting genus/subgenus is limited to compounds reduced to practice; disclosure not commensurate in scope with genus/subgenus claimed
- (iii) Common structural attributes of the claimed genus, combined with a correlation between structure and function, is neither disclosed in the instant application nor commonly known in the art.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

(Enablement)

73 Claims 1-4 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of the compounds made and tested for KSP inhibition, does not reasonably provide enablement for using the compounds not supported by the disclosure. The

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specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8USPQ2s 1400, 1404 (Fed. Cir. 1988). MPEP 2164.01(a) states “There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue”. The factors are applied below to the instant claims.

The breadth of the claims

The claims are drawn to products of Formula III with the scope as defined in section 6.I.

The nature of the invention

The genus of compounds are claimed to possess KSP inhibiting activity.

The state of the prior art/level of ordinary skill/level of predictability

The level of ordinary skill is high, but the level of predictability in the art is low (section 6.III). There is no art known correlation between structure/function for this class of compounds. Absent guidance, one of ordinary skill would not expect that the entirety of compounds embraced by the genus would possess KSP inhibiting activity. One of ordinary skill would not know which of the compounds not exemplified, if any, would possess the claimed activity.

The amount of direction provided by the inventor/existence of working examples

The compounds of claims 5 and 6 are disclosed to possess KSP inhibiting activity (see also above, section 6.II).

The quantity of experimentation needed to make or use the invention

The skilled artisan would be subject to undue experimentation to determine which compounds of the broad genus claimed, if any, would possess KSP inhibiting activity in order to practice the invention commensurate in scope with the breadth of the claims.

Claim Rejections – 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-4, 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The 14th option for R¹⁰ is claimed to be oxo. In view of the core structure for Formula III in claim 3, it is not possible to substitute oxo onto any carbon atom in the phenyl ring without violating the valency requirement.

The 16th option for R¹⁰ is claimed to be (N=O)R₁₂R₁₃. It is not clear what structure this substituent refers to. As drawn, the nitrogen is perceived to be double bonded to oxygen atom, single bonded to R₁₂ and R₁₃; thus, exceeding the valency allowed.

Allowable Subject Matter

9. Claims 5 and 6 are allowable over the art of record. The closest structures in the prior art (Lariff et al., CAPLUS AN: 1984:482038, RN 91307-94-7) does not meet the limitations for R⁸ and for the 2,5-dihydropyrrole core.

Conclusions

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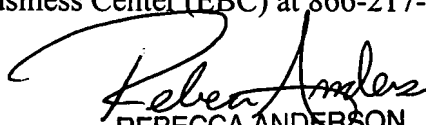
10. Claims 5 and 6 are allowable.

11. Any inquiry concerning this communication should be directed to Sun Jae Y. Loewe whose telephone number is 571-272-9074. The examiner can normally be reached on Monday through Friday from 7:30 am to 5:00 pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Cecilia Tsang (571) 272-0562, can be reached. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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